

## **II. REMARKS/ARGUMENTS**

### **A. Status of claims**

Claims 38 and 47-52 are currently pending. Claims 1-37 and 39-46 were previously cancelled. Claim 38 has been amended without prejudice. It is respectfully submitted that no new matter has been added by virtue of this amendment.

### **B. Information Disclosure Statement**

Applicants wish to take this opportunity to thank the Examiner for entering into consideration the patents and publications (with the exception of reference "BR", as discussed below) listed in the January 25, 2006 (re-submitted April 11, 2006) Information Disclosure Statement.

The Examiner stated that "one publication cited therein, designated BR, lacks a publication date" and that "[w]hile the other patent and other publications cited therein, and supplied, therewith, have been considered as to the merits, these three publications have not." (Emphasis added)

In response, Applicants have submitted herewith replacement sheet 2 of the form PTO-1449, which includes the publication date for reference "BR". Applicants note that this is the only reference listed on the January 25, 2006 form PTO-1449 which did not include a publication date. Therefore, Applicants respectfully request that the Examiner consider reference "BR", as the publication date has now been provided.

### **C. The Examiner's indication that the previous arguments are unpersuasive**

The Examiner indicated that the previously submitted arguments are not found persuasive. Applicants will address the Examiner's reasons below:

#### **I. Applicants arguments do comply with 37 CFR 1.111(b)**

The Examiner stated that "Applicants recite that their claims are limited to the recited ingredients but don't assert that any of the references require more than these two 'essential' ingredients."

Applicants respectfully submit that such an assertion was made in the previously submitted arguments. Applicants point out that the two "essential" ingredients of the present claims are meloxicam and oxycodone. As discussed in Applicants' previous response and further discussed below, the prior art references require ingredients different than these two essential ingredients, namely, (1) ibuprofen (required by Baker); (2) caffeine (required by Sunshine); and (3) the NSAID's which fall within the five structural categories as described in Sunshine.

## **II. The Baker reference does not describe other NSAIDs**

The Examiner stated that "the fact that the Baker reference described some of the other NSAIDs as 'somewhat inferior' likewise does not preclude a holding that finds the claimed invention obvious."

Applicants respectfully submit that Baker reference, does not describe any NSAIDs other than ibuprofen in the description of their invention. The only reference to NSAIDs is in reference to the "selected NSAIDs" of the Sunshine reference in the prior art, which does not teach or suggest meloxicam.

Applicants respectfully request that the Examiner cite the passages of the Baker reference which purportedly describe "some of the other NSAIDs as 'somewhat inferior'" in order for Applicants to further address this matter.

## **III. The Baker reference does not test other NSAIDs**

The Examiner stated that "the Baker reference merely states that ibuprofen was unexpectedly better than the other NSAIDs tested, which implies that the other NSAIDs also

functioned to improve analgesic activity albeit to a lesser extent."

Applicants respectfully submit that the Baker reference does not provide any indication that other NSAIDs (besides ibuprofen) were tested.

Applicants respectfully request that the Examiner cite the passages of the Baker reference which purportedly describe the testing of other NSAIDS in order for Applicants to further address this matter. In the event that the Examiner was relying on the Background of the Invention to make this statement, Applicants again note that the "selected NSAIDs" of the Sunshine reference do not teach or suggest meloxicam.

**IV. The non-preferred embodiments of Baker do not teach or suggest the claimed invention**

The Examiner stated that "[a] reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill in the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories." (Citations omitted).

Applicants respectfully submit that the invention in Baker is the purported unexpected synergism of ibuprofen and opioid analgesics. In support of this statement, the Examiner is directed to column 2, lines 11-14 the Baker reference which states the following:

According to the present invention there is provided a pharmaceutical composition comprising a combination of (a) a narcotic analgesic...and (b) ibuprofen..."

The preferred embodiments of the Baker reference are set forth, e.g., at column 2, lines 44-47 which states the following:

Oxycodone, oxymorphone, hydrocodone and hydromorphone are preferred...Oxycodone is most preferred.

Accordingly, contrary to the Examiner's conclusion, the "non-preferred" embodiments of the baker reference all include ibuprofen. In view of the above, the nonpreferred embodiments include ibuprofen and a narcotic analgesic other than those which are listed as preferred.

Therefore, Applicants respectfully submit that the embodiments of the Baker reference (both preferred and nonpreferred) do not teach or suggest the presently claimed invention.

**D. Rejection under 35 U.S.C. 103 (a) over Baker et al., Engelhardt et al., Engelhardt and Distel et al.**

In the Advisory Action, the Examiner maintained the rejection of claims 38-39, 46-48 and 50 under 35 U.S.C 103 (a) over US 4,569,937 (hereinafter "the Baker reference."), Engelhardt et al. Inflamm. Res. 44:423-433 (1995) (hereinafter "the Engelhardt et al. reference"), Engelhart Brit J. Rheumatol. 1996:35 (suppl.1):4-12 (hereinafter "the Engelhardt reference"), and Distel et al. Brit. J. Rheumatol. 1996:35(suppl.1):68-77 (hereinafter "the Distel reference").

Applicants respectfully submit the combination of cited references does not teach or suggest the presently claimed invention. With respect to Baker, this reference does not teach or suggest the use of "NSAID's" and further does not contemplate any NSAID other than ibuprofen.

In the Advisory Action, the Examiner stated that Baker et al. teaches pharmaceutical compositions comprising "ibuprofen (a non-steroidal anti-inflammatory drug or NSAID)" and cited the Baker reference at column 1-2.

Applicants note that column 2 of the Baker reference makes no mention of the term "NSAID". Applicants further point out that the relevant portion of column 1 of the Baker reference states that "[t]his patent discloses that the analgesic effect of the combination of a selected NSAID and a selected narcotic analgesic is greater than for either alone." The phrase "this patent" actually refers to U.S. Patent No. 4,464,376 issued to A. Sunshine et al. (hereinafter

"Sunshine"). A copy of Sunshine is enclosed herewith as Exhibit A. Applicants note that the two references to the term "NSAID" at column 1, lines 17-27, are the only recitations of the term "NSAID" in the entire patent, and they are with reference to the teachings of Sunshine. Applicants submit that the purported invention in Sunshine is directed to combinations of caffeine and NSAIDs; caffeine and narcotic analgesics; and caffeine and NSAIDs/narcotic analgesics. Applicants respectfully submit that the present claims exclude the presence of caffeine by virtue of the "consisting of" terminology in the claims.

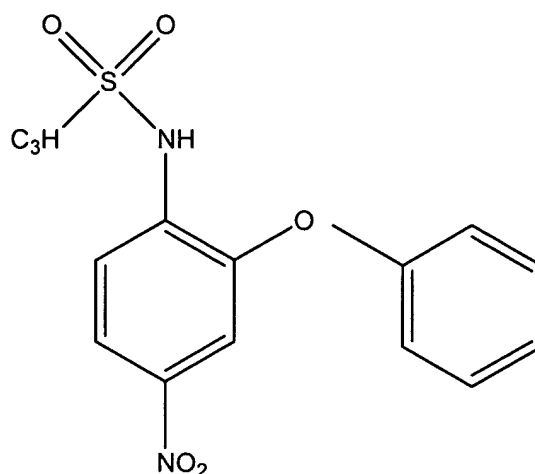
Furthermore, the Examiner's attention is directed to Sunshine at column 14, lines 58-61, which recite "[t]he term 'selected NSAID' as used herein is intended to mean any non-narcotic analgesic/nonsteroidal anti-inflammatory compound **falling within one of the five structural categories indicated hereinabove.**" (Emphasis added).

These five categories are set forth at column 7, lines 42-50 of Sunshine which states that:

The non-narcotic analgesics/nonsteroidal anti-inflammatory drugs for use in the compositions and methods of the present invention can be selected from the following categories:

- (1) the propionic acid derivatives;
- (2) the acetic acid derivatives;
- (3) the fenamic acid derivatives;
- (4) the biphenylcarboxylic acid derivatives; and
- (5) the oxicams.

The chemical structures of the (5) categories are exemplified in columns 8-11. Applicants submit that the chemical structure of the presently claimed NSAID, *i.e.* nimesulide:



does not fall within any of the five structural categories indicated above. Therefore, even assuming arguendo that Baker contemplates the use of other NSAIDs based on the reference to Sunshine, Applicants submit that the "other" NSAIDs would be limited to the five structural categories listed in Sunshine and would not include nimesulide.

The Examiner further stated that:

The Baker et al. reference teach that dose ratios can be adjusted and that the analgesic activity of the combined oxycodone and ibuprofen activity is 'unexpectedly enhanced' or synergistic i.e. the resulting activity is greater than the activity expected from the sum of the activities of the individual components, thereby permitting 'reduced dosages of narcotic analgesics' (e.g. oxycodone) AND which diminishes adverse side effect (e.g. addiction) and toxicity which would result from the otherwise required amounts of the individual drug components resulting from high dosages of oxycodone or NSAID's such as ibuprofen. See e.g. col. 1-2; col. 3, lines 19-32.

Applicant's respectfully point out that the mention of NSAID's at column 1, as discussed above, is in reference to Sunshine which describes the enhanced analgesic effect resulting from the combination of NSAID's with caffeine. Also, as discussed above, there is no mention of NSAID's at column 2. Applicants further point out that column 3, lines 19-32, recites the following:

Application of an equieffective dose substitution model and a curvilinear regression analysis utilizing all the data for the individual compounds and various dose ratios for the combinations establishes the existence of unexpectedly enhanced analgesic activity of combinations of oxycodone and ibuprofen, i.e., the resulting activity is greater than the activity expected from the sum of the activities of the individual components.

As can be seen from the above cited passage, the Baker reference does not state that the enhanced analgesic activity occurs from "NSAID's such as ibuprofen", as improperly inferred by the Examiner, but rather solely from ibuprofen.

Further, Applicants submit that the Examiner has not shown any motivation to substitute ibuprofen for meloxicam. The Examiner stated that "one of ordinary skill in the art would have been motivated to substitute meloxicam (a NSAID) for ibuprofen (a different NSAID) in the Baker reference compositions in light of the Englehardt et al., Engelhardt and Distel et al. reference teachings that meloxicam is at least equally efficacious." However, there is no suggestion in the Baker reference to substitute ibuprofen with any other NSAID, let alone meloxicam. Moreover, the only NSAID's alluded to in the Baker reference are the NSAIDs which fall into one of the five structural categories described in Sunshine and thee reference does not teach or suggest meloxicam.

Furthermore, Applicants submit that the Examiner is applying an improper "obvious to try" rationale in suggesting the substitution of ibuprofen with meloxicam. "In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Applicants submit that *In re O'Farrell* is analogous to the present situation, where one of ordinary skill in the art would have to try each of numerous possible NSAIDs in place of

ibuprofen in order to arrive at the selection of meloxicam, as the Baker reference gives no direction as to what NSAIDs other than ibuprofen would be successful.

The Examiner also stated that "the instant situation is amendable to the type of analysis set forth in *In re Kerkhoven*, wherein the court held that it is *prima facie* obvious to combine two (or more) compositions which is taught by the prior art to be useful for the same purpose." (Citations omitted). On the contrary, Applicants submit that the instant situation is not amendable to the type of analysis set forth in *In re Kerkhoven*. The prior art does not teach the claimed combination of meloxicam and oxycodone. To apply to the analysis set forth in *In re Kerkhoven* would result in a formulation having the compositions of the cited references, *i.e.* a combination of meloxicam and ibuprofen and oxycodone. The present claims exclude the presence of ibuprofen.

Applicants also submit that Baker teaches away from the use of NSAIDs other than ibuprofen, based on Baker's discussions of the synergistic effect between ibuprofen and narcotic analgesics, and the absolute absence of any reference to other NSAIDs which may be used in the Baker formulation. In further support of this position, the Examiner is respectfully directed to column 1, lines 6 - 9 of Baker which states as follows:

*This invention relates to pharmaceutical compositions of narcotic analgesics and ibuprofen having analgesic activity in mammals, and to methods of use of the compositions to alleviate pain in mammals.*  
(Emphasis Added)

The Examiner is also directed to column 2, lines 11-15 of Baker which states as follows:

*According to the present invention there is provided a pharmaceutical composition comprising a combination of (a) a narcotic analgesic, or a pharmaceutically acceptable salt thereof, and (b) ibuprofen, or a pharmaceutically suitable salt thereof,...*  
(Emphasis Added).



Applicants further note that ibuprofen is the only NSAID mentioned throughout the entire reference, and it is the only NSAID exemplified in the Baker formulations.

In view of the above, not only would one of ordinary skill in the art not be motivated to substitute the ibuprofen of the formulations of Baker with meloxicam in view of Baker et al., Engelhardt et al., Engelhardt and Distel, Applicants submit that Baker teaches away from the use of all other NSAIDs other than ibuprofen. Accordingly, it is respectfully requested that the 35 U.S.C. 103(a) rejection over Baker et al., Engelhardt et al., Engelhardt and Distel et al. be removed.

**D. Rejection under 35 U.S.C. 103 (a) over Baker et al. Baker et al., Engelhardt et al., Engelhardt and Distel et al. in view of Oshlack et al. (US 5,472,712) or Oshlack et al. (US 6,294,195)**

In the Office Action, the Examiner further rejected claim 49 under U.S.C. 103 (a) over Baker et al., Engelhardt et al., Engelhardt and Distel et al. in view of US 5,472,712 (Oshlack et al.) and US 6,294,195 (Oshlack et al.)

This rejection is traversed. It is respectfully submitted that the Oshlack references do not cure the deficiencies of the Baker reference in view of the Engelhardt et al., Engelhardt and Distel references as set forth above.

Accordingly, it is respectfully requested that the 35 U.S.C. 103(a) rejection over Baker et al., Engelhardt et al., Engelhardt and Distel et al. and Oshlack et al. be removed.

**III. CONCLUSION**

In view of the foregoing, it is believed that the application is now in condition for allowance, and applicants respectfully request such action.

The Examiner is respectfully requested to contact the undersigned at the telephone number provided below in the event that a telephonic interview will advance the prosecution of the application.

Respectfully submitted,

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